clear treatment benefit regardless of your protein C status at baseline.

The way we rationalize that is when we administer activated protein C, we are really giving pharmacologic doses of a recombinant protein, to achieve pharmacologic concentrations. The concentration of APC in blood now is about 50 nanograms per ml. Basically, it is unmeasurable in the severe sepsis population and actually unmeasurable, at least by our assay, with the limit of detection of about 10 nanograms in healthy subjects.

So, I believe that what you are seeing is the pharmacologic benefit of achieving pharmacologic concentrations.

DR. SIEGEL: I would also like to address the question itself and something underlying the assumption of the question. That analysis you saw defined "deficient" and "not deficient." If you look at page 34 of our briefing document, there are pre-specified analyses that broke down protein C classification in more detail. Those might suggest that there are some interactions. Are those interaction P values underneath? I am not sure. There are P values underneath of 0, 0, 0, .00001 for unordered analysis of these different subgroups, but it is not a relatively straightforward situation.

In fact, the best relative risk was in those

people with normal protein C and those people with the lowest protein C. So, if the question is is the evidence restricted to the population with abnormal protein, with protein C deficiency, that is what the slide we showed addressed. There is nothing to support that.

If the underlying assumption of your question as you worded it is is there any evidence suggesting that protein C might interact with drug effect? Well, there is certainly some suggestion, but in ways that, you know, would require a more complex hypotheses to try to get at.

DR. MACIAS: If it is helpful, we did the protein C analysis as a continuous variable and the interaction P value was .7.

DR. RELLER: Dr. Archer, do you have one final question before we hear the response to the functional status, the data that were being gathered by Dr. Macias? No. Okay.

Dr. Macias, the answer to the earlier query.

DR. MACIAS: I just wanted to make one quick question to help Dr. Murray and that is we did a fairly extensive pharmacokinetic analysis of the BDS2, BDS2+ data in the pivotal Phase 3 trial and the pharmacokinetics are absolutely the same between the BDS2 and BDS2 compound, just to help you with your question about had it been tested in other animals.

I believe Dr. Wald had two questions. The first one was what was the relative risk for the first APACHE quartile in patients under the amendment. The mortality for the APC group was 9.5 percent. The mortality for the placebo group was 13.9 percent and the relative risk is .68 for patients in the first APACHE quartile. That is about 250 patients.

The second question was what was the status of patient location and the distribution for home is 29 percent of patients and 29 percent of patients under the original protocol, 29 percent of patients in the placebo group, for home, 30 percent of the treated patients are home and under the amended, 31 percent of the placebo are at home and 32 percent of the treated are at home. So, the same absolute difference.

There is one additional point about the relative risk over time that might be helpful and throughout the course of the trial as we kind of alluded to, sites that didn't enroll well during the first part of the trial were discontinued. It is not that they enrolled necessarily bad patients, but they just didn't enroll any patients or enrolled one or two and those sites were discontinued.

Toward the end of the study, we actually had completed a separate, a different study with anti-inflammatory, but that protocol actually utilized the same

inclusion criteria and many of those sites were actually then rolled over into our EVAV(?) study and that kind of happened in the last six months, eight months, of the trial.

That is about the only other thing that has really come up as we have looked at the mortality curves over time.

Then one last question, could we just make just one -- take a minute for Dr. Bernard just to address the pediatric question very quickly?

DR. RELLER: Final comment from Dr. Bernard and Lilly and we will have one question from Dr. Rotello and Dr. Fleming, you had a question -- no. Okay. Dr. Rotello, you had a question after this.

DR. BERNARD: Thank you, Dr. Lindblad, for your presentation. I want to make a couple points based on the questions which you asked in your presentation that were not brought out in the initial presentation.

First of all, there are no randomized control trials in pediatrics and we all agree to that. The real issue that pediatricians here can attest to is there really cannot be a randomized control trial in pediatrics with this indication.

Could I get Slide No. 86, please?

The reason is this. If we assume a 12.5 percent placebo mortality rate, that is assuming a drug effect of 20 percent relative risk reduction, an alpha two sided of .05

and even with 80 percent power, we would need a study of over 5,000 patients in order to prove in a randomized control trial that this would have an effect.

In contrast, because of the limited number of pediatric patients and the low incidence of severe sepsis. The largest trial ever done in pediatric critical care -- and this was a sepsis trial -- was 396 patients, which occurred over four years. A randomized trial cannot be done.

Even if you assume a 20 percent mortality rate, like for kids of Wiginton, who you heard testify, we would still need a trial of over 3,000 patients, which by the way if started today would end at the end or over my expected life expectancy as a human being. We are talking about trials that would occur over several decades.

I think that is why we have the wisdom in the law that is the law in the Code of Federal Regulations, which is Core Slide No. 88. Dr. Lindblad said we need to prove that they are the same in pediatrics and in adults and that is really not true. The statute says that we need to prove that they are sufficiently similar.

I would really suggest to you that these are sufficiently similar in most ways. Now, he brought up several different aspects, which he thought they were different.

Could I have Slide No. 129, please?

A major point was made in terms of organ dysfunctions. I will explain where this slide came from. The organ dysfunction data presented by the Agency was based off the inclusion criteria for the trial. The inclusion criteria for the trial were designed only to give great similarity between the adult and the pediatric study. We measured organ failure by typical organ failure indices that are known and routinely used in pediatrics that were not the same as the inclusion criteria of the trial.

This was prospectively defined. It is by Wilkinson in The Journal of Pediatrics, 1987. When you look at the data for real organ failure, the way pediatricians define it, what you see is there is great similarity. Yes, there is more cardiovascular than adults, but instead of being half the amount of respiratory organ failure, there is actually slightly more.

I would suggest that these are very, very similar. If you go to the next slide, please, if you look at the numbers who had one, two, three or four organ failures, what you see is that the pediatric patients did not have more one organ failure, but actually had almost the same or even more. In fact, the mean number of organ failures were 2.7 in pediatrics, which is very similar to that in adults.

Core Slide No. 92.

What is important is not that there are differences, but are the differences relevant. I would suggest to you, based on the data that the effect of Drotrecogin Alfa is independent of whether you have one, two, three, four organ failures. They were all within the point estimate. It is also independent of whether you have gram negative, gram positive or no culture infection.

Very importantly for pediatrics, the pathophysiology is the same. There are some differences, but the pathophysiology is the same. There is still a decrease in protein C levels, a universal increase in D dimer levels, as well as a drop in anti-thrombin III. The inflammation coagulation paradigm, the induction of innate immunity is the same.

Can I go back to back up Slide No. 92, please?

I use this slide as similarities of infection, not differences of infection. Again, Drotrecogin had an effect, whether it is gram positive, gram negative or mixed and the pediatric population is very similar. The reason you see more gram negatives is because of meningococcemia.

Pediatricians are enrolling patients who have a high risk of mortality, the kinds of sick patients that you heard about. Thirty percent of the patients in Part 2 of the study had fulminate meningococcemia. Now, again, we say is a blood stream infection. Of course, its origin is in

the respiratory tract. But I would say that this is sufficiently similar and, remember, the adult Phase 3 data has results that are independent of the type of organism, which caused it.

The last couple of slides, please, No. 95.

There was a suggestion that the adverse events between the pediatric data and the adult data were the same and nothing could be further from the truth. In the adult data, all clinical manifestations -- I am sorry -- in the pediatric data, all clinical manifestations of severe sepsis were collected as adverse events. This is very different than the collection mechanisms that were done in the adult trials.

Could I have Slide 97, please?

For example, in the pediatric study, the most common adverse events were those that you see in sepsis, particularly thinking about 30 percent meningococcal disease, generalized edema, lung edema, oliguria bradycardia, hypokalemia, thrombocytopenia. These adverse events are all adverse events of severe sepsis.

Slide No. 101, please.

There was a bleeding risk in pediatric patients, but this also occurred in the patients who had the most organ dysfunction. In other words, there is no such thing as a free lunch. The sicker patients, which are more likely

to benefit also had the higher risk of severe adverse events. If you look at all patients, the mean organ failures at baseline was 2.7. With SAEs(?) was 3.3. If they had a bleeding SAE, they had four organ failures in pediatrics, which is a very high number and, again, those who died were similar in the amount of organ failures.

So, there was no dissociation. There was clearly a relationship, again, on small numbers. But the sickest patients get the most adverse events and you would expect that.

Finally, Slide No. 101.

The child who, quote, died of an intracranial hemorrhage -- and, again, we could go through all four of the severe adverse events. Two of them occurred during the course of an infusion. This was documented on Day 13. Now, this may have been an intracranial hemorrhage associated with Drotrecogin Alfa. It may have been.

We do know, however, that in puerperal fulmanants with meningococcal disease, there is that baseline risk of intracranial hemorrhage, somewhere between 2 and 5 percent. That is precisely what we get when you combine the meningococcal patients and puerperal fulminants patients.

Of note, this patient had puerperal fulminants on multiple ionotropes(?) and a baseline platelet count of 26,000. Yes, that patient was at very high risk of

bleeding, but also according to the data at very high risk of benefit. The drug was stopped due to anisocoria. But if there was thought to be a very large intracranial hemorrhage, I would point out one thing, that even after APC was stopped, the child was systemically heparinized for CVVH(?), which occurred for many, many days.

It was not until Study Day 13 that the intracranial hemorrhage was documented postmortem. So, this child did die with an intracranial hemorrhage. Whether it was associated with APC or not is of question. It might have been associated. It may not have been.

The child was heparinized and was at very high risk for intracranial hemorrhages, based on the baseline severity of illness. So, overall, the main point is this: The wisdom in the law is obvious. There cannot be randomized controlled pediatric trials due to numbers.

Are the populations sufficiently similar? Absolutely. The pathophysiology is extremely similar. The minor difference is in the types of organisms that cause that pathophysiology are irrelevant. The organ failure data, when you look at real pediatric organ failure scores are exact.

Thank you.

DR. RELLER: Dr. Rotello, did you have a question before we go to the questions and discussion?

DR. ROTELLO: Yes, one for the sponsor.

You have chosen to stratify your data by raw PACU(?) scores. There is not necessarily a linear correlation between a PACU score and predicted mortality. Have you calculated the predicted mortality for your group based on -- compared to actual mortality for both the study group and the placebo group?

DR. MACIAS: The way we collected the APACHE, we were not able to convert APACHE to predicted mortality. First, we didn't collect the APACHE within the first 24 hours of admission to the ICU and, second, we didn't collect the reason for ICU admission that you need to generate the coefficient that gets plugged into the equation because the intent was never to use the APACHE to predict mortality. The intent was to compare the baseline severity of illness.

DR. SENEFF: I am Mike Seneff. I am director of critical care at George Washington University. I just want to use one thing, Leo, to address that.

It has been made clear that APACHE II was not collected per the normal methodology in the study. This was referred to earlier and I just wanted to make sure that everybody was clear that this refers -- this slide looks at the first APACHE II quartile and looks at the location of the patients prior to hospitalization, not prior to randomization.

So, even though 83.5 percent of the Drotrecogin Alfa patients came in from home and 82 percent of the placebo patients came in from home, that was when they were hospitalized, not necessarily when they were randomized. So, they could have been in the hospital for five days before they got their APACHE II score. If those patients are not randomized appropriately across the two groups, that could lead to why the placebo mortality was so low in the first quartile.

So, the methodology here of this 20 year old system was not collected in this study as it was validated and calibrated in these studies that were done 20 years ago.

DR. RELLER: The time has come. I have already given the charge to the committee. We will deal with the questions and discussion related thereto.

Agenda Item: Discussion and Questions

The questions and the format are on our agenda sheets. I have been asked to read some sections as preludes to the question, so that we have this captured on the tapes, as well as serving as a focus for the discussion. I will point out where we expect discussion and those comments then being used by the Agency and I will delineate when we are going to have a vote on a specific question.

I. Patient entry criteria. Data supporting the efficacy of drotrecogin alfa (activated) were derived from a

single Phase 3 randomized, placebo controlled trial of nearly 1,700 adult with severe sepsis. Treatment resulted in a significant reduction in Day 28 all cause mortality compared with placebo treated patients, 25 versus 31 percent.

Eligibility required meeting three or more SIRS criteria, at least one of five organ failure criteria and with evidence of infection. Midway through the trial, the eligibility criteria were modified to more clearly exclude patients, who had a high probability of dying from an underlying non-sepsis-related condition within the 28 day study period.

As a result of the modifications, fewer patients with malignancy, chronic APACHE II health points, those who were immunocompromised, et cetera, were enrolled.

Questions for discussion: Please comment on entry criteria and the implications of the modified criteria. Do the entry criteria define a population appropriately described as having severe sepsis?

We will go around the table of the voting members, which are all, except for FDA persons at the table, and will follow the pattern of left to right and then the next question will go the other direction.

Dr. Archer -- I am sorry -- Dr. Leggett is first.

DR. LEGGETT: In terms of comments about the entry

criteria, they follow the things for SIRS and with the organ system failures in that 60 percent had four of the SIRS criteria. However, there was only one to two multi-organ system failures in 57 percent of the patients, mostly hypotension or respiratory criteria.

I note that we clinically have a very difficult time differentiating ARDS from pneumonia. I was a little concerned about that.

My feeling of the way things worked is we sort of have a sigmoid E-max curve in all of these biological functions. If you are off to the 80 percent or more most severe portion of that E-max curve or you are under the 20 percent or less, it is very difficult to show a change by the addition of a new drug. So, I think that the way they modified their protocol allowed them to move into that 20 to 80 percent relatively linear time frame of what kind of drug effects you would do and that allowed them to show a change and an improvement in outcome.

That still doesn't help us very much about real life situations of what we are going to do with that group, that is the 80 percent or above and the group that is 20 percent or below and, to me, the sponsor's interpretation is sort of at odds with the FDA's interpretation of what that lower group risk is.

We are still left without knowing what to do about

that high risk group, who got kicked out of the original protocol. So, I think that, to me, even though this is called severe sepsis, it is in that middle range of severe sepsis, if you will.

DR. RELLER: Dr. Archer.

DR. ARCHER: Yes. Thank you.

I understand why the modification was made. I think it was appropriate in order to include more appropriate patients with sepsis in the protocol, but as was just said, I don't think that defines the group of patients, who are ultimately going to get this product if it is approved, which are the more severely ill patients and many of the kind that were kicked out of the study.

I don't know how to reconcile those two. I think that is part of the problem that we are going to be dealing with through the whole time talking about this product. So, I think it did define a population of patients with severe sepsis, but without underlying disease, but it may not have defined a population of patients that we see in the hospital as having severe sepsis.

DR. RELLER: This is not a vote. This is for discussion only.

Dr. Cross.

DR. CROSS: Well, clearly, patients here had satisfied entry criteria for severe sepsis. However, within

that broad category, especially with the amendments made, I am not left with a good feeling of knowing whether or not there is a definable population, who would benefit from this drug.

Many of the patients who were excluded are precisely those who would be most likely treated in my large, academic center. There are those who are immunocompromised with underlying malignancy, et cetera, et cetera. So, although there were some entry criteria used here, it would not really define how it would be used in my hospital. I still am left with not knowing what were the reasons for the change halfway through the protocol, which resulted in the differences reported.

DR. RELLER: Dr. Chesney.

DR. CHESNEY: I thought the entry criteria did define a population described as having severe sepsis and I thought I heard Dr. Macias say that they didn't really change the criteria. They just tightened them up, if you will. I think the decisions or answers to the later on questions are going to be at either end of these populations, if that makes either sense, those who were excluded and those who are APACHE score II.

So, that is my comment.

DR. RELLER: Dr. Christie.

DR. CHRISTIE-SAMUELS: It seems to me that in real

life that the patients that I see in ICU are much more ill than the patients that we are seeing here that were studied, based on cases, like 50, 60 percent in baseline populations. Whereas, I think the study is quite appropriate. They did everything they did with approval. The question is how do you generalize that a normal population that we take care of on a day to day basis? That would be my concern.

DR. RELLER: Dr. Ramirez.

DR. RAMIREZ: The question is to find a population with severe sepsis. That answer is clearly "yes." We just follow the recommendations that we use nowadays to define severe sepsis. The question is -- and Dr. Archer already asked this, from the pooled population of severe sepsis, not looking at inclusion criteria, but looking at the exclusion criteria, from the 100 percent of the population with severe sepsis, how many patients want to be excluded with these exclusion criteria.

The inclusion criteria is very clear to me on defined severe sepsis. The problem is that the exclusion criteria limited the number of patients with severe sepsis to a very selected group of patients. When we look at these selected group of patients, clearly defined they have severe sepsis and they were able to at least I think it was whatever to define these populations, the same population at any other time, compared with positive cultures, positive

infection.

The inclusion criteria is clear. My problem is that it is too large an exclusion criteria. I have to translate these exclusion criteria to clinical practice, but I think that this is not part of the question. But there is an advantage for the patients that were defined according with the study protocol.

DR. RELLER: Dr. Ebert.

DR. EBERT: I agree with the previous panel members that suggested that the definitions are reasonable for a definition of severe sepsis, but that will have difficulty projecting these criteria onto an appropriate use for patients if and when this drug is approved.

One other addition is that there did appear to be a smaller percentage of patients in the treatment group after the protocol modifications, receiving activated protein C, who do not resuscitate patients. So, there may have been a greater emphasis on treating patients because of the smaller percentage that were do not resuscitate.

DR. RELLER: Dr. Wald.

DR. WALD: I think that the study did define an appropriate group of patients with severe sepsis. I think the challenge here will be like it is for many other drugs, for us to design and describe the patients who are most likely to benefit, rather than to use it indiscriminately

and I think that is a -- we have for many other categories of drugs restrictions and we have either committees or groups that need to decide that a particular drug is indicated for a patient. I think we could handle it in the same way.

DR. RELLER: Dr. Wittner.

DR. WITTNER: I agree with what has been said before by the previous panelists. I do believe that this -- the study did define a population of patients, who should or who could benefit or might benefit from this protein C, activated protein C. The problem is who will in practice actually receive this medication is really the question in my mind, since I think some of the major criteria, at least at our hospital, such as immunosuppression, would be, I think, if those people are left out, we would lose a large percentage of the individuals in our group.

DR. RELLER: Dr. Murray.

DR. MURRAY: I agree and I think the real issues will come up in the labeling and the licensing and the criteria so that you do not set a precedent for future equivalent studies to be judged as equivalent for groups that haven't yet been shown to be efficacious.

DR. RELLER: Dr. Fleming.

DR. FLEMING: I think the entry criteria do define a population having severe sepsis in appropriate

populations. The concerns that I have have been clearly articulated already. My general philosophy is clinical trials ought to be designed to obtain the relevant real world answers. Hence, we should tend toward inclusive eligibility criteria.

There should be a very close relationship between the eligibility criteria and what the label is. As I read page 2 of the executive summary, it is my sense that the sponsor is clearly asking for a wider indication and we have heard some of the specifics. We have heard specifically higher risk patients, I presume they would be restricted to higher risk for bleeding, pediatrics. So, I am particularly concerned if, in fact, there is an intention to use these data to justify a label that, in fact, is much more inclusive than what the eligibility criteria were in the trial.

DR. RELLER: Dr. O'Fallon.

DR. O'FALLON: I don't think I have anything to add to this question.

DR. RELLER: Dr. Munford.

DR. MUNFORD: Yes, I think the criteria did define a population with severe sepsis. However, it was a very narrowly defined population as others have said, may or may not extrapolate to the larger pool of patients with severe sepsis.

DR. RELLER: Dr. Rotello.

DR. ROTELLO: I agree with the previous panel members that these do define an appropriate population for sepsis. I do have issues with restricting patients' entry based on a disease process that might not result in their death during this hospital visit. I believe that that is more appropriate than the actual disease, the severity of it.

DR. RELLER: Dr. Warren.

DR. WARREN: It seems to me that since the entry criteria changed halfway through the trial and the efficacy also seemed to change, it will be difficult to come up with appropriate guidelines because if you eliminate those, such as immunosuppression, you are essentially doing a subgroup analysis, which is not really, perhaps, the best approach. On the other hand, if you include the entire group, then you are eliminating the fact that the efficacy was much greater with the second group defined.

DR. RELLER: Dr. Suffredini.

DR. SUFFREDINI: You know, my concern is that we basically have two studies. We have entry criteria for one, entry criteria for two. There are overlap certainly, but in terms of -- and they define a very sick group of patients, but in terms of generalizability, et cetera, we really are competing one against the other study, basically, and not

until the second part of the study where there were many things changed, inclusion criteria, drug change, among other things, I think we have concerns about combining the two studies.

So, yes, the criteria defined a sick group of patients, but it is a moving target and I am not sure why the sponsors changed their target midway through the trial. In other words, with the knowledge that they have had with extensive clinical trial experience, why it had to be modified, I don't know the reason. I really don't -- I didn't really understand the rationale behind that.

DR. RELLER: Dr. Lilly.

DR. LILLY: I do find that infected patients with systemic inflammatory response syndrome and evidence of organ dysfunction to meet the criteria for severe sepsis. I would also like to point out that targeting this therapy to patients, who are going to die from sepsis is appropriate.

DR. RELLER: Dr. Carcillo.

DR. CARCILLO: I would like to for the most part limit my comments to the pediatric study, since that is my expertise and there really isn't enough information in the pediatric study for me to comment intelligently on this. Thank you.

DR. RELLER: Dr. Eichacker.

DR. EICHACKER: I think that the inclusion

criteria in both parts of the study or in both studies do describe a sick group of septic patients. In terms of defining or in terms of assessing what the significance of the change in the exclusion criteria were, which was the big change between the first and the second part of the study, I don't know how to assess it because the agent changed also.

I don't know whether differences that we see in the second part of the study, how much of that is related to defining a group of patients better as opposed to potentially changing the drug. So, I don't know how to assess what happened to the inclusion criteria.

DR. RELLER: It seems to me we have basically two studies here and even though the study design may be appropriate in inclusion of sepsis in both groups, we have heard much that there is nothing to say that they couldn't be combined, but then we are left with quite different outcomes.

One of those two still baffles me. If they are really not so different, then why the differences? I am wondering if the first phase may not be more reflective of what physicians in intensive care units actually have to deal with.

II. Treatment effect in subgroups defined by disease severity. The reduction in mortality was not consistent against all prospectively defined patient

subgroups. The data suggest that there may be a different mortality effect in less severely ill patients with better survival prognosis. Mortality in patients with the lowest APACHE score quartile was higher in the activated protein C group compared to placebo patients and a smaller treatment benefit was observed in those in the second APACHE II quartile compared with patients who were in the third and fourth quartiles, as shown in the table and the figure that is before you.

Question 2: This is for discussion and then we will come to 3, an actual recorded vote by committee member. So, for discussion.

Dr. Fleming -- we are going to come to each person.

DR. FLEMING: I am wondering if we could have permission to -- since, at least, I have withheld all statistical comments on the issue of subsets, could we -- and I don't want to answer the question yet, but would it be timely to give statistical discussion before we start answering the question? Since we have heard from Dr. Siegel, we have heard from Dr. Lindblad and we have heard from Dr. Helterbrand, but we haven't heard from the statisticians on the committee yet.

DR. RELLER: Why don't we do this? I will read the Question No. 2 and then we can have the statisticians

comment go first. Would that take care of it?

DR. FLEMING: Good.

DR. RELLER: Please comment on the implications of the analysis of treatment effect and disease severity, the mortality by quartile subgroup analysis. Should the sponsor conduct further clinical controlled studies of the effects of the activated protein C in patients with severe sepsis and more favorable prognosis, lower APACHE II scores?

So, what we want here is the comment first from our biostatisticians on the committee and then how the rest of the committee members, guests see this.

Dr. Fleming, first.

DR. FLEMING: Great. Let me give -- let me ask my colleagues as I am beginning if you -- you might turn to pages 135 and 136 of the sponsor's briefing document. As you are doing so, my general sense is there is much wisdom in what we have heard from Dr. Helterbrand from the sponsor and there is much wisdom in what we have heard from Drs. Forsythe and Siegel from the FDA on this issue, the former giving us a sense to be incredibly cautious about interpreting lack of effects in these lower risk patients, the latter, the FDA commentators, raising key issues.

I think there is a lot of truth in what both of them are saying. First of all, Dr. Helterbrand is exactly right, that there is tremendous hazards to overinterpreting

subgroup analyses. Far more often than not in my own sense, it is more heat than light. There is a lot more variability. You are breaking studies down into smaller numbers and the trials simply aren't designed to adequately address effects in those smaller numbers.

So, if you do have a common effect, clearly, when you look at subgroups, it is very likely that confidence intervals will overlap equality, as Dr. O'Fallon was pointing out. It is also even likely, as Dr. Helterbrand was pointing out, that you might see subgroups with point estimates that show no effect.

Conversely, however, there are those settings in which treatment effect truly does depend on patient characteristics and these subgroup analyses can be very insensitive to picking up those effects and the sponsor's argument that the APACHE II low group is something that we should ignore or not be overly concerned about because the confidence interval just barely includes a 20 percent reduction is a very insensitive test as well.

If there is, in fact, no effect, there is a very high chance, even if there is no effect, that that confidence interval will overlap a 20 percent reduction. So, where does that leave us? It leaves us possibly in a setting where it is very difficult to interpret subgroup analyses. So, should we not do them?

Well, I think that is absolutely indefensible because clearly there can be signals and there certainly be settings in which treatment effect and relative benefit to risk can depend on patient characteristics. There are a higher level of structure that we have to look into the data, though, to be able to have a better sense of separating the light from the heat.

Some of the criteria that we have looked at are strength of evidence and there has to be a lot more statistical evidence to justify a subgroup analysis; a second is biological plausibility, as Jay Siegel was talking about before lunch, and a third criterion is confirmation. What I would like to do is draw your attention to pages 135 and 136, acknowledging that these data are still from my own perspective somewhat troubling, but I do see more signal and confirmation here as was indicated in the FDA presentation.

What I would like to draw your attention to is the right hand column on pages 135 and 136 because the right hand column tells you how effectively each of these covariates is really distinguishing a low risk group from a high risk group. What you will see is the vast majority of these covariates are not separating the population into groups that have more than a twofold difference in the risk of mortality.

So, indeed, Dr. Helterbrand is correct. If you

look at all of the covariates that we are assessing here, then you can't simply see one subgroup that doesn't show an effect and overreact to that. But the fact of the matter is most of these covariates are not highly predictive, are not distinguishing low risk groups.

In fact, what stands out is that if you are looking on pages 135, clearly, the APACHE II covariate and the organ failure covariates are very effective in a risk gradient in establishing high risk groups and low risk groups in contrast to the IL6 on page 136, which is not nearly as effective in establishing high risk gradient and low risk gradient.

In addition, on page 4 of our handout from the FDA -- I won't call your attention -- you don't need to go to that, but, in fact, when you divide age up by decades, you also see a covariate that has substantial gradient. Interestingly, all three of those covariates that are the most effective in distinguishing truly low risk patients, i.e., those with one organ failure, those that are younger and the lowest APACHE II group do all show the same consistent signal of lesser effect.

It has been argued, ignore the APACHE II because it is not validated. I can't think of a better validation than the right hand column. Look at the actual data in the trial. In the data in the trial, did these patients by

APACHE score have strikingly different survival? Much more so by APACHE than by IL6.

So, in essence, what I do see is a very -- I do see a consistent signal of validation. It doesn't prove anything to me, but it does -- this is a higher order of investigation that goes beyond Dr. Helterbrand's presentation. There is a consistent signal here that I see that, in fact, has been put forward in the FDA discussion.

Now, Question No. 2. How does this impact Question No. 2? Specifically, is there need for essentially further studies in these low risk patients. I would put forward in my own thinking several factors as I would try to answer that. First of all, what is benefit to risk?

These patients that are in the lowest APACHE II grouping have about a 12 percent mortality. Even if in truth there was a 20 percent reduction, that translates into two or three deaths per hundred people versus the six that we have been told about for the broader group. Two or three deaths is certainly relevant, but it is a smaller overall benefit. That is presuming that there is, in fact, as the sponsor would argue or as somebody who says there is a homogeneous effect would argue, that assumes that we have a 20 percent reduction.

Of course, as the data show, there is a 25 percent increase. So, there is a leap of faith there to argue that

there would even be two deaths per 100 people. So, there is a smaller unmet need. It is still a significant need, but it is a smaller unmet need in that group.

Secondly, there is some consistency of evidence that in these lower risk patients, the effect may be much less. Thirdly, there is a non-trivial safety risk. That safety risk is in part represented by these SAE bleeds. There were nine of them. Four of those people died. That is a 2 percent death rate.

It may not be that those deaths with major bleeds were entirely mediated through the effect of the treatment, but if, in fact, they were substantially mediated so that you had four deaths, that is 2 percent, that would exactly offset the 2 percent benefit, which, in fact, we didn't see, but in a best case scenario, if we argued there wasn't an interaction, we would say would be there.

Finally, and I don't have a good sense about this, but the additional evidence of the 1 1/2 percent risk of intracranial bleeds that was referred to by the FDA in the more recent data also becomes more of a concern in a low risk population. The lower the risk the population, the lower the overall net benefit. Hence, the bigger concern with the level of side effect.

DR. RELLER: Thank you, Dr. Fleming.

Dr. O'Fallon. And for other members of the

committee, I think we will have the comments from the statisticians and we are actually going to take on what are clearly succinct questions having to do with the need for -- possible need for further studies and also the next question, we will have votes on both of those. So, everyone will have a chance to vote on these.

We will hear the overarching statistical comments and then anybody who has a general comment before we actually take the two votes here.

Dr. O'Fallon.

DR. O'FALLON: Dr. Fleming was nearly as eloquent as this when he came to work for me after the completion of his doctorate degree several years ago. How could I possibly add anything to that eloquent presentation?

DR. RELLER: Are there any other comments from committee members to other committee members having to do with things that they would like -- any other statistical comments? Okay.

Now we will go to Dr. Eichacker. The question that we will vote on next is as follows: Should the sponsor conduct further controlled clinical trials of the effects of drotrecogin alfa (activated) in patients with severe sepsis and a more favorable prognosis; for example, lower APACHE scores?

DR. EICHACKER: I am not going to add to what has

already been said. I think that this is very important, not just because of the reasons that have been stated, but, again, I think this is a very difficult trial to interpret, given the way criteria changed and given the way drug changed. So, I think it is very important that it continue to be studied.

DR. RELLER: That is a yes?

DR. EICHACKER: That is a yes.

DR. CARCILLO: I think that the drug should be studied in a randomized controlled fashion in the low risk population of pediatrics. The reason I have been asked is because of our expertise in the epidemiology. There are, in fact, 45,000 to 47,000 cases of severe sepsis in children per year. Dr. Gerard(?) is really referring to meningococcus, which is only 1 to 2 percent of severe sepsis in the country.

DR. RELLER: Dr. Lilly.

DR. LILLY: I do not believe that there should be additional studies based on APACHE II scores, particularly not the way in which they were calculated by the sponsor. Such scores are not clinically applicable and would constitute a significant expense with very little real patient gain.

DR. RELLER: Dr. Suffredini.

DR. SUFFREDINI: My sense is that, yes, further

trials should be done in terms of verifying what was seen in the second study and the issues of risk in terms of underlying risk, whether you are a high risk patient or a low risk patient needs to be examined because that is, in fact, what will be done in clinical practice.

DR. RELLER: That is a yes?

Dr. Warren.

DR. WARREN: I learned that the way to approach this is a hypothesis-driven trial and a confirmatory trial and I think that what we have seen is a hypothesis-driven trial that has given us some hypotheses. So, I believe that, yes, there should be further studies, but I am not sure they should only be in the subgroup of the lowest APACHE. I think they should be in defined groups that maybe has not been parsed out yet.

DR. RELLER: Dr. Rotello.

DR. ROTELLO: I find it very difficult to interpret the APACHE scores in the first portion of the study. You wind up having an APACHE score, which is weighted towards chronic health evaluation points. When you add the modified criteria, you eliminate some of those disease processes, which would give you chronic health evaluation points. So, that second portion is weighted toward the acute physiology of scale. I don't think they are comparable.

So, I think further studies do need to be done.

DR. RELLER: Dr. Munford.

DR. MUNFORD: Given the disparate results and the two phases of the trial and the fact that there is not an obvious explanation for these differences, I favor further study of this drug. I think that study should incorporate some estimate of disease severity, whether it is the APACHE II score or some other scoring or prognostic system. So, yes.

DR. RELLER: Dr. O'Fallon.

DR. O'FALLON: I am going to try to answer the question directly asked, in contrast to most of the answers that I have heard so far. Absolutely not. There is no evidence that the difference would be substantial enough for anything other than a huge, huge study, which would be impractical and expensive beyond belief, to make any progress. So, I do not believe that a study should be conducted on those with the APACHE II lower quartile scores, which is the way I read this.

DR. RELLER: Thank you.

Dr. Fleming.

DR. FLEMING: This is a difficult issue. I believe there is need for more data and whether or not that additional data is inclusive of higher risk or people with less favorable prognosis we will discussing later. I

believe there is need for additional data in patients that are -- that have a more favorable prognosis. As Dr. O'Fallon points out, this would be an extremely significant undertaking with the very large sample size and maybe we can talk about that later. But I believe there is need for independent confirmation in more favorable prognosis patients and I would include in that the pediatric population.

DR. RELLER: Dr. Murray.

DR. MURRAY: Yes, I agree with that completely, except that I am not sure how it is going to be done and if it can be done and in the meantime, I think, yes, in an ideal world, I would love to see more data on that population, but can you really get it in any kind of reasonable fashion?

DR. RELLER: Dr. Wittner.

DR. WITTNER: I believe that further data should be acquired, especially for the lower APACHE group. I think it is necessary in view of the changes in the protocol, both in terms of the drug and in terms of the admission criteria.

DR. RELLER: Dr. Wald.

DR. WALD: I think if we were looking at just the patients who were entered into the amended protocol, we would not be having this dilemma because I think that the results were more striking and more consistent with each

other. So, in that sense, I feel like this drug is getting a little bit of a bad rap for a very rocky beginning. Although the patient group was selected, again, I think that is all right. I think we have to be the judges of how we use a drug and that we can't not accept it because it is misused by others.

I think we sort of have to set the standard for the patients who are most likely to benefit. So, I feel comfortable with the drug as is if we write the right indications and I do think we need to do the specific study in pediatrics.

DR. RELLER: Dr. Ebert.

DR. EBERT: I do not feel that targeting a specific low risk population and conducting further studies in that population would be appropriate. Most of the data to date suggests that the higher risk populations are where we are seeing the greatest benefit and I agree with others that have said that this would take a very large study and may not show a difference.

DR. RELLER: Dr. Ramirez.

DR. RAMIREZ: I listened to the sponsor. I listened to the FDA and I think that I liked the consideration of the FDA that not only that decreased mortality has been clearly shown with the APACHE scores more than 25 when you have more than one organ failure with the

patient in shock. I think that there is a population that we can collect in hospitalized patients with sepsis without shock with a lower APACHE score with just one organ failure to define because essentially this is going to use a statistical evaluation that still is unclear. But I agree that they are the most important indicators that relate to severity in favor of no advances in mortality who use the drug.

Then I would not only look at the APACHE but the other indicator of severity.

DR. RELLER: Dr. Christie.

DR. CHRISTIE-SAMUELS: My answer is yes. I would study patients with a more favorable prognosis. I think we would be able to get some more information, which might be a little bit more -- would be better extrapolated to children. I don't think we necessarily have to look at the APACHE. We could look at other things. We could look at severity of illness, more about the different types of organ function or malfunction and age.

Thank you.

DR. RELLER: Dr. Chesney.

DR. CHESNEY: To me, this is the crux of the issue of all the questions because I would be very reluctant to take a patient group that has a good outcome, the best possible outcome of all the groups and yet has from what I

understand a worse outcome in terms of bleeding and significant adverse effects. So, I would either exclude patients who would fall into the APACHE first quartile from being able to use this drug or I would get more information.

DR. RELLER: Dr. Cross.

DR. CROSS: I appreciate the arguments on the -- that was an interesting biologic signal on the APACHE scores, but I would not do a study just to address that point, but I firmly believe we do need more data to find out whether or not the drug works. So, I think as part of a new acquisition of data, perhaps, the -- some appropriate assessment of risk might be incorporated into that kind of trial.

DR. RELLER: Dr. Archer.

DR. ARCHER: I am persuaded by the eloquence of the statisticians that it would be a waste of time and money to do answering specifically this question to go after just the APACHE I score population group. So, I would say no.

DR. RELLER: Dr. Leggett.

DR. LEGGETT: Last and probably least, a couple of points. I think the sponsor, I believe, this morning showed us a slide of how all the post hoc evaluation of subgroups then got turned -- was proven wrong on confirmatory trials. So, I think we are in the same problem here. Unless we do that confirmatory trial, we are not going to know. But I

would not limit it to the low risk group as has been pointed out, because we would have to enroll too many people, which is why they amended the trial to begin with.

But I think that if we combined the covariates that were pointed out to be the ones that most differentiated the high risk, low risk and just go right down the median as was done in some of the FDA approvals, that might be a way to get patients into the trial and use smaller numbers.

In that regard of several things pointing out the same difference, the FDA on page 33 also shows that the groups that had a relative risk of less than .8 were those who had the most organ failures and they had the highest APACHE scores. So, I mean, I think there is yet more consistent data to say that we need to look at that farther.

My final question is is it possible for the FDA and the sponsors to get together after this and talk about something that disturbed me a little because I thought I heard the sponsors say there are actually three groups of patients in this trial because at the very end when we saw the drop in the mortality rate was when they started rolling in patients from other trials even though the inclusion were the same. So, now we have got three groups instead of two and that worries me.

So, I guess I think further study is needed and

pediatric studies are needed.

DR. RELLER: Yes, for the record. But what I mean by "yes" is I am not convinced that there isn't a group of patients who may suffer harm rather than benefit from this drug. That may include pediatric patients, who start out with a lower risk in the first place. It think that needs to get sorted out. Whether it is sorted out by exclusion in labeling and is done postmarketing or whether it is done with additional studies that encompass the full range of risk up front, which would be my preference, there are other practical realities that have to go into that.

My worry is that there are patients we don't yet know exactly how to define that may not derive benefit.

Now, the mirror image of the Question 2 that we just had is Question 3 and we will answer it first and then we will come back to suggestions on how, depending on how the vote comes out, whether A or B is further delineated.

If licensed, should the indication for drotrecogin alfa (activated) be limited to the subset of patients with severe sepsis, who have a poorer prognosis?

Dr. Leggett.

DR. LEGGETT: Again, this is a mirror image of what I think I just tried to say and that is that we can't make any real life decisions knowingly well without -- by just doing subset analysis. So, I think that we should not

just limit it to the patients with poorer prognosis.

DR. SIEGEL: I am sorry. Could you repeat that comment?

DR. LEGGETT: Like it not, the trial has been run. So, the question is we then further limit it based on just the poor prognosis, folks, we have done a post hoc analysis of subgroups. On the other hand, I think that the indications should, as closely as possible, mirror the entry criteria so that we should not expand the licensing beyond what was described in the entire group of this patient group.

DR. RELLER: We will come back to -- there will be more discussion of this issue depending on the weight of the committee, the prevailing opinion. But if this drug were licensed, should there be -- should its use be limited to those in the -- those with a poorer prognosis by some defined criteria, APACHE 2nd, 3rd, 4th quartile, et cetera?

Dr. Siegel, a little -- we are here for one purpose and that is to provide guidance to the Agency. So, you focus what you want to have answered and we will try to do the best we can.

DR. SIEGEL: Thank you.

Crafting questions is always very difficult. You never know how the discussion is going to go. I noticed on the last question, there were lots of "yeses" and several

"noes," all for very different reasons. So, I wouldn't even know how to add those up in numbers.

But as far as this, of course, it is always difficult to figure out the right order to ask questions. We haven't yet asked about whether the drug should be approved because we wanted to make sure there was discussion of some of the other pertinent issues before we get there, but really what we are trying to get at here is a practical issue, which is that if this drug is approved, if we mae that decision based on our review on the advice of this committee, would the -- should the indication statement be simply severe sepsis as proposed by the company or should we somehow define a population within that that is more severe or somewhat more limited and then if so, how would that be described?

B just raises an issue that if there is a need for an indication that covers, particularly if it mentions the mortality benefit in a broad population, often it raises pragmatic issues in terms of then studying further studies in that population.

DR. RELLER: Does that help, Jim?

Basically, the way I see this question is it leaves open for the moment as to whether more studies are going to be done or recommended to get there, but, basically, given what we have now, could this be licensed as

the sponsor requested or would want some constraints or focus on that to the higher risk groups? Now, how you do that, I think, is subject -- that is another issue.

Is that correct, Dr. Siegel? That is what you want?

DR. SIEGEL: That is correct. Assuming we can make a decision based on data available now to approve this, would the committee advise that it be approved as suggested for all severe sepsis or rather for some subset?

DR. RELLER: The way this question, this part, has been framed is for more severe sepsis. So, basically, a restricted approval, if approved at all. That is to try to clarify things.

Dr. Leggett.

DR. SIEGEL: We are cautious about the word "severe" simply because everybody in this trial, even those in the lowest quartile have severe sepsis as defined.

DR. RELLER: Dr. Leggett.

DR. LEGGETT: What I meant by that group is I agree if you can restrict it, but I think it is already being restricted by the lack of immunocompromise of the patients at higher risk of bleed and all that sort of thing. Patients with underlying diseases were excluded from the second half of the trial.

So, I think that in that sense, yes, it is

restricted, but I do not think in the Part B that we should no longer conduct a placebo controlled trial in a population with less poor prognosis because that is exactly the question that you were trying to get at is is it really a 2 percent gain in a 1.5 percent intracranial hemorrhage.

DR. RELLER: Help Tom. He has to -- yes or a no?

DR. LEGGETT: Part A, it should be limited to the subset that they studied. I thought I had said that before. Part B is there should be further placebo controlled trials in the lower group.

DR. SIEGEL: So, an indication for the low risk group but they should be studied more.

DR. LEGGETT: Exactly. I don't think we should do the subset of only what was described as the higher -- the three and four APACHE II, greater than two organ failures. That, I think, is what we do as clinicians when we come up with our own guidelines for our own cities.

DR. RELLER: Dr. Archer.

DR. ARCHER: I think what he is trying to say is that, yes, it has to be restricted on the basis of the studies that have been completed so far. I mean, we have -- the data we have is limited by how the study was designed and I think it is going to have to be restricted to those patients who were studied. So, therefore, yes, there should be restrictions, yes, I think it should be restricted to the

severest quartile, but that is going to still eliminate a lot of the sickest patients who have sepsis because they weren't studied. That is the immunocompromised patients, et cetera, et cetera.

That is the group on whom, I think, more studies are needed.

DR. SIEGEL: Let me provide a little bit of clarification about labeling here. You know, it is a general principle that people are reluctant to generalize beyond entry criteria of a trial. But I can assure you that the indication statement in the label on the way drugs are used are never strictly limited by the entry criteria. You are not likely to see an indication statement, it would certainly be pioneering, which included what the platelet levels and all other lab tests might need to be for most drugs, even those that are frequently used as an entry criteria.

I might hypothesize, although the advice of this committee might be persuasive otherwise, that it would be difficult to capture in an indication statement, per se, an indication statement for the drug, the exclusion of patients. One could conceivably write that it is contraindicated or not indicated in patients who have chronic underlying disease. We would rarely write a contraindication unless we thought there was harm and the

limited data on 80 patients suggests that that is not the case.

So, we might well, since the committee is quite concerned about this, that if we approved the study, highlight that issue in the description of the clinical study. What this question is getting at -- and I know this committee is very concerned about the patients with underlying disease, but I would like to get clear advice n this question of what to do about the low risk patients, not low risk as defined by whether they had chronic, underlying disease, but low risk as defined by the various indicators, all within the group of this study.

If we approve the drug, should we write a broad indication for all severe sepsis, which I imagine would preclude studying low risk patients further or should we in some way modify that statement to indicate that it is indicated in the higher risk -- in higher risk, higher probability of poorer prognosis, poor prognosis for mortality, whatever wording one might choose or work out. So, in a way that might reflect, as clarified in the clinical study section these concerns that we have discussed about the risk predictors and the effect by risk predictor.

DR. RELLER: I am going to take the chairman's prerogative and record my vote as a possible model for how this might be tackled.

My answer is yes, because I am concerned that the lower risk group -- there is some effect of this drug and that effect is in the higher risk patients. I think that one has to reserve judgment on its utility in those assessed objectively somehow to be at lower risk in the first place. Basically, it is complementary to the first answer. So, the answer is yes, because I don't think the data allows a general approval at this time.

Dr. Archer.

DR. ARCHER: I think that is what I said earlier as well. I think that exactly mirrors what I said. Yes. Thank you.

DR. RELLER: Jim, is that the intent of where you want to go? We will let you think about it and we will get a yes or no later.

Dr. Cross.

DR. CROSS: I will follow the chairman and say yes. Having said that, I am reminded of similar types of meetings almost a decade ago with other anti-sepsis drugs, in which there was a very strong tendency not to go into the area of subgroup analysis, but rather to treat the whole population of, quote, septic-appearing patients.

But here I think that we do have -- I think there is something going on at both ends of the spectrum, both in the lower, less risky patient and in the more severe one.

Furthermore, Dr. Fleming pointed out that we do have at least three separate things, which may be helpful to clinicians in the future, who may want to use this drug in terms of actually assessing degree of risk. That is the age APACHE score and organ failure.

So, I would say that, yes, a study ought to be done not just on the poor prognosis, but also on the less sick ones and trying to validate the utility at least of those three strong predictors, perhaps, of patient risk.

DR. RELLER: Thanks.

Dr. Chesney.

DR. CHESNEY: I would say yes, it should be restricted to those patients in the quartiles 2, 3 and 4, as defined by the study. I would put in the label that the group that were excluded in this study have not been studied. We really don't know what would happen in those patients that were excluded with the amended criteria.

DR. RELLER: Dr. Christie.

DR. CHRISTIE-SAMUELS: My answer is yes and definitely the patient -- that should be included are those who are in the third and fourth APACHE II quartile. Those who have laboratory evidence of DIC, those not on heparin, those who are over 50 years of age, those who have two or more organ failures and those who are in the lower risk group, there is a risk of hemorrhage. We are not sure.

DR. RELLER: Thank you.

Dr. Ramirez.

DR. RAMIREZ: My answer is yes. I just want to -- I have a problem with the question still limited to a subset of patients with severe sepsis who have a poor prognosis. We discussed that the second part of the protocol was an attempt to eliminate patients with more severe sepsis that was due to comorbidity. They were looking for patients with more severe sepsis that was due to sepsis and then their definition here of sepsis, severe sepsis, with poor prognosis, I would read this as my patient immunocompromised -- this is not the patient that we are discussing.

You can have severe sepsis due to the sepsis itself or severe sepsis due to your comorbidity and the patients with severe comorbidity were excluded, just to confuse a little that question.

DR. RELLER: Dr. Ebert.

DR. EBERT: Based on the information presented today, as well as the relative risk/benefit in the various risk groups, I would vote yes.

DR. RELLER: Dr. Wald.

DR. WALD: I think this is really tough to answer. I do feel somewhat persuaded by the data after the amendment was made that, in fact, this is not hazardous in the less severe groups. So, I would say I think more study is

needed, but for the moment, I would, I think, recommend its use in all patients -- patients in severe sepsis who were studied.

DR. RELLER: Dr. Wittner.

DR. WITTNER: Who am I to argue with the group. I do believe that the protein C should be used with individuals in severe sepsis, who have the poorer prognosis, but I think more studies really need to be done on individuals who were in the late exclusion group, since I think these are a major component who we see in the ICUs.

DR. RELLER: Dr. Murray.

DR. MURRAY: I am going to vote no in terms of the restriction with respect to the APACHE, but I think that some sort of modifying statement, disclaimer, black box, something needs to be said that in that group, the data are -- cannot make a decision that there are data to the contrary.

But, yes, in terms of the exclusions for the patients that were not studied. I think that those -- there needs to be some continued exclusions on those and if this is a very expensive drug, I think that hospitals, HMOs and managing corporations -- it may be like enrolling a patient on a study to use this drug in someone. One may have to, indeed, go through a lengthy form. So, I think that there will be -- should be and probably will be other exclusions.

DR. RELLER: Dr. Fleming.

DR. FLEMING: If this is licensed, I would agree that there should be -- that the indication should be limited restricting to the -- ruling out those more seriously ill patients that were excluded by the eligibility criteria and also the patients that have the more favorable prognosis. I don't think the question specifically ties us down to whether that is the first quartile of the APACHE. I think that is something that we -- that I would advise be considered very carefully by the FDA, but I do believe that if licensed now, the indication should be limited to exclude those patients that would have the most favorable prognosis.

DR. O'FALLON: I also believe that it should be restricted. So, I am voting yes.

DR. RELLER: Dr. Munford.

DR. MUNFORD: I am going to be a contrarian, I suppose. If I would answer the question as written, that is, if licensed, should the drug be limited, I would say no. The reason is that -- it is a historical reason and I think that we need to be careful not to establish a double standard.

For all the previous trials in this field, the drugs have seemed like they were probably going to work, but not quite and subgroup analysis was done to try to figure out the groups in which the drug did work. Then subsequent

trials were designed to test the hypothesis generated from the first trial and as Dr. Opal showed us this morning, no drug in this field has reproducibly protected patients with severe sepsis.

Here the situation is different. It looks like the drug may have worked and we are using subgroup analysis to try to figure out who it didn't work in. I don't think that is quite fair. I think if the drug is licensed, I think it needs to be licensed for use in essentially patients in whom it was tested and regardless of subgroup analysis, but I would emphasize two points.

One is I strongly favor more studies of this drug and, secondly, that if it is licensed, I strongly favor limiting the use of the drug to the patient population in which it was tested and not a more general license.

DR. RELLER: Dr. Rotello.

DR. ROTELLO: I also vote no. I believe that if it is licensed, it should not be restricted just for severe sepsis. I think basing a use of something on prognosis puts too much variability into the individual clinician's hands to deal with. Also, in those patients who have mild sepsis, there will be a subset of those who will progress to severe sepsis without any way to predict that. If you wait to treat those patients until they become severe, you have given them a much worse chance of survival.

DR. RELLER: Dr. Warren.

DR. WARREN: I also would vote no for very much the similar reasons as Dr. Munford has mentioned, that I think this was a hypothesis-driven trial ultimately. I would also like to point out that there are a lot of different subgroups that are similar. For instance, the drug didn't seem to work as well in the surgical patients as the medical patients and how will we decide based on this one particular group of APACHE as opposed to all of the other subgroups that we haven't even gotten to. Why this group? Why not exclude surgical patients? Why not exclude age?

So, for those reasons I vote no. But I do think there should be more studies.

DR. RELLER: Dr. Suffredini.

DR. SUFFREDINI: To the first part, I would vote yes. Yes, it should be limited and I think that while we talk about subgroup analysis, there is at least compelling information that age, organ failure, the severity of illness, as reflected by a score really makes your risk/ benefit ratio, it will vary with what your underlying problems are.

So, yes, I would limit it and to the Part B, I would yes and it should be restricted to patients with much poorer prognosis and we should study more of it. I mean, we

need more information.

DR. RELLER: Dr. Lilly.

DR. LILLY: I agree with the sentiments of others that there should be better clinical science in this area. I vote no. I respectfully point out that the trial itself demonstrated that individuals who met these entry criteria have a substantial mortality benefit. The trial was not designed and I do not believe provides informative information on subgroup analysis.

Therefore, I think to put the overinterpretation in front of the interpretation is a mistake and that the labeling should allow patients who meet the entry criteria of this trial to have access to the drug.

DR. RELLER: Thank you, Dr. Lilly.

Dr. Carcillo.

DR. CARCILLO: I vote that in patient groups where there has been a randomized controlled trial done that there not be any limitations in its labeling. However, if the FDA were to decide to approve the drug in a population where a randomized control trial was not done, then I think that it should be expected that the possibility of increased intracranial hemorrhage should be discussed with the patient or the patient's family before prescription.

DR. EICHACKER: Again, to sound like a broken record, I look on this as two studies. We actually haven't

been shown data or we have not been shown these subgroups for the two different parts of the study. So, I am not even sure we can say what the relationship is between severity and the effect of the drug, although I believe there probably is such an influence. I would have to say yes, but it is really not having seen the data that provides a basis for that answer.

DR. RELLER: Thank you.

The subparts A and B, most members have already commented on those. Is there any additional comment from any committee member on the A and B components of this question?

Like the sepsis syndrome that is very complicated, these questions and their interpretation, but I think we are actually getting there and we are moving in the right direction of getting things out on the table and we will be coming to a bottom line later.

Okay. Now, III, the treatment effect in patients with disseminated intravascular coagulation. Activated protein C has anti-thrombotic and pro-fibrinolytic analytic properties that may contribute to its mortality effects in patients with severe sepsis. Thus, one might see different effects in patients with sepsis who have DIC from those who do not. The majority of patients in the trial, more than 90 percent, had evidence -- and this has been brought up what

the definition is -- let's leave it at evidence of altered coagulation -- at study entry, as defined by the presence of two or more of the following laboratory findings that are listed for you.

Now, of note, two individuals did not have altered coagulation at baseline and 113 in whom insufficient laboratory data were available to determine their status. There was little suggestion of treatment effect. So, where we want to go now is should Drotrecogin Alfa (activated) be further evaluated in controlled studies in patients with severe sepsis, who do not have laboratory evidence of DIC?

Dr. Siegel, could you clarify for us if -- we want something so that we don't get into a protracted debate on what constitutes DIC. Could you give us a standard or some definition or should we phrase it in terms of what was actually included in this trial?

DR. SIEGEL: I am glad you asked for that clarification. The question as became clear in the discussion earlier and in the review in recent weeks. What was called DIC, at least for the purpose of this analysis, is not even by rigor of lab criteria and certainly by clinical criteria, necessarily what would normally be diagnosed or even in a textbook definition of DIC.

The question we are basically asking with Question No. 4 is given that there is only 115 patients in the -- who

didn't meet these criteria and even in those patients, we don't know that they didn't meet them, we -- in all but two of them, simply the lab tests were not available and given the concept raised by several speakers before, the drugs should be indicated for use in patients who are studied. The question is is there a population using these definitions, who don't meet these definitions, who either need to be studied or need to be excluded or I think one of the questions is do they really exist in significant numbers. That is something we have been trying to get at.

So, once again, I may not have made that black and white, but I guess the simple answer to your question is using the definitions that were used, is there a need for further study of people who didn't meet that criteria since so few were studied here or is it just not that important an issue?

DR. RELLER: Dr. Eichacker, comment, please.

DR. EICHACKER: I would say yes. I think that these reflect -- again, they are part of -- they reflect the severity of infection and to the extent, I believe, that the influence of severity of infection has to be studied here and this would be patients who don't have abnormalities of these parameters probably have very mild sepsis since I think that these generally reflect evolving sepsis.

So, I think, yes, they should be studied.

DR. RELLER: Dr. Carcillo.

DR. CARCILLO: I defer.

DR. RELLER: Dr. Lilly.

DR. LILLY: While more information in this group would be very desirable, their rarity makes study impractical.

DR. RELLER: Dr. Suffredini.

DR. SUFFREDINI: I would agree actually. I think this is a rare entity, that anyone who is infected will not have at least two of these four criteria. So, I think it is not an important question.

DR. RELLER: Dr. Warren.

DR. WARREN: I would agree. It is not an important question. I would point out, though, that we don't know whether this drug only works in the coagulation box. So, I think in future studies if there are some, it should studied -- there should not be a question. It should be studied in all patients. It shouldn't be necessarily an entry criteria.

DR. RELLER: Dr. Rotello.

DR. ROTELLO: I agree. I don't think any further evaluations are necessary. The rarity would make it impractical.

DR. RELLER: DR. Munford.

DR. MUNFORD: I don't think it deserves further

study. I also -- I think we heard from the company this morning that almost all these unknown people simply didn't have measurements done. So, they very well may have met these criteria, too. So, I don't think it is a big issue.

DR. RELLER: Dr. O'Fallon.

DR. O'FALLON: The rarity makes it impossible and, therefore, they should be allowed to be treated in answering this question.

DR. RELLER: Dr. Fleming.

DR. FLEMING: I think what I am about to say has already just been said, but I believe it is -- these small numbers of people have unknown status, which I see as very different from having clear documentation of a different effect in a known cohort of patients without DIC.

My sense is there isn't sufficient evidence here to be restrictive in any way in a decision about approval. However, if future studies are done, as some of us have suggested would be useful, gathering additional data about this would certainly be useful as well if it is already planned to do future studies.

DR. RELLER: Thank you.

Dr. Murray.

DR. MURRAY: I agree. Nothing additional.

DR. WITTNER: Likewise. Nothing additional.

DR. RELLER: Wald.

DR. WALD: I agree.

DR. RELLER: I agree.

DR. EBERT: I also agree.

DR. RAMIREZ: I think that it won't be necessary. Now, the question is if these patients find out they don't have DIC according to the criteria or we don't know if they have DIC? What is the --

DR. SIEGEL: 113 of these 115 patients didn't have all the lab tests drawn. There have been some -- they were required by entry. So, it may well be that they are a random population. There has been some speculation that the lab tests are more likely to be drawn in people who are, for example, showing bleeding evidence of DIC. So, they may be less likely to have DIC, but in the most part, we just don't know.

DR. RAMIREZ: Because at the same time almost -- the low risk, low severity patients and then these patients -- we identified these patients low severity, also patients with no DIC and we agree that by definition if you have severe sepsis, you have to have low inflammatory activity. Then the lack of DIC can be a definition of the patient's non-severe sepsis. We are looking at the low severity patient with APACHE or lack of shock or just one organ failure. It may be that the definition of severe sepsis that we use in one organ failure is too sensitive and the

patients don't have DIC because they don't have severe sepsis.

I agree that these need to be probably further studied, but not specific for indication for the drug.

DR. RELLER: Dr. Christie.

DR. CHRISTIE-SAMUELS: No. Rarity is impractical. However, in uncontrolled studies, yes.

DR. RELLER: Thank you.

Dr. Chesney.

DR. CHESNEY: I think they don't need to be further studied because they would fall in the low risk group and I would exclude the APACHE I from the indications.

DR. CROSS: I concur not to study them.

DR. RELLER: Dr. Archer.

DR. ARCHER: I agree.

DR. RELLER: Dr. Leggett.

DR. LEGGETT: I concur not to further study it and I would like to point out that the times I have been here, this committee has never been entirely inherently incoherent in its responses to different questions.

DR. RELLER: Dr. Siegel, do you want any comment from the committee members regarding a future -- when future studies are done of a different approach from what was done in terms of definition of altered coagulation? In other words is there a group of patients with a strict definition

that would be generally acceptable for DIC that would be worthy of inclusion in future trials? Or do you have a sense of what you need to -- for this question?

DR. SIEGEL: At the heart of asking this question was, in fact, did they use the right definitions and did they treat a typical sepsis population or did they treat one that has a lot more coagulopathy than your typical population? I think those questions were asked.

As to how best to design future studies with respect to coagulopathy, I could imagine quite a lot of fruitful discussion of that issue with the expertise at this table that it is perhaps not a critical question to the decisions we are facing.

My inclination on your question would be to proceed through the rest of the questions and open the floor at the end for any further advice that any members of the committee would like to give on that or other related topics.

DR. RELLER: Thank you.

IV. Treatment effect and heparin use. Many patients received low dose heparin for prophylaxis of DVT. Both heparin and Drotrecogin Alfa (activated) have anti-thrombotic effects. Mortality was lower in patients who received the compound than in those receiving placebo regardless of whether low dose heparin was used, but the

treatment effect was several fold greater in patients not on low dose heparin, as shown in the table.

If the differences in activated protein C in patients on low dose heparin, 3 to 4 percent, and patients not on low dose heparin, 9 to 15 percent, are real, then the question of whether to administer low dose heparin when using this compound could be very important. Potential mechanisms by which low dose heparin might influence the Drotrecogin Alfa (activated) effect include the low dose heparin may provide some benefits, leaving less residual benefit for the addition of the activated protein C and low dose heparin might abrogate some of the benefits of Drotrecogin Alfa (activated) perhaps through synergistic toxicity.

Question -- and we will vote on this -- should more studies be done addressing whether and how low dose heparin should be used in patients receiving Drotrecogin Alfa (activated)?

Dr. Leggett.

DR. LEGGETT: First, a point of clarification. Is this before consideration of licensure or afterwards or does it matter?

DR. SIEGEL: I think the question would be valid either way. Of course, if it is broadly licensed without further randomized studies -- no, I take that back. The

studies we have potentially been looking at here are studies in which -- I mean, it could be worked into a controlled study but it could also be done in a study where all patients get APC and you randomize to whether to give low dose heparin or not.

So, this question would be fully relevant either way.

DR. LEGGETT: That was exactly where I was going because if I understood things correctly, this trial was not designed to look at the effect of low dose heparin and by doing it, we are once again going into this post hoc analysis, which bothers me.

There are other things that could be looked at, though, in the future and I think there could be a randomized trial, but, you know, if somebody comes up with protein S, can we throw protein S in there? You know, there are a lot of questions that could be talked about later, but in the view of whether this needs to be done before licensure is decided upon by you guys, I do not think it is necessary.

But the broader question, is this an important question to look at is what we are trying to --

DR. SIEGEL: I think so.

DR. RELLER: Dr. Archer.

DR. ARCHER: I think this is one thing that can be

studied and should. I think the idea of a trial, everybody gets protein C and then you randomize them to get low dose heparin. It would be a good trial. I mean, this is a common therapy in these patients and I think it really does need to be studied. So, I would strongly say yes.

DR. RELLER: Dr. Cross.

DR. CROSS: I think it is an important question that ought to be studied, but not limiting the licensure issue.

DR. RELLER: Dr. Chesney.

DR. CHESNEY: I agree totally. I don't think it should limit licensure, but I think it could be studied after.

DR. RELLER: Dr. Christie.

DR. CHRISTIE-SAMUELS: I agree.

DR. RAMIREZ: Yes, I agree. It needs to be studied, but even though -- let me ask one question. Is the activated -- because I imagine that a low dose heparin in all these patients to prevent DVT and is the activated protein C prevent DVT by itself during infusion?

DR. RELLER: Dr. Macias.

The difference between DVT and the active compound at -- and placebo was 2 and 3 percent.

DR. MACIAS: At 3 percent of the placebo group, 2 percent in the Drotrecogin Alfa (activated) group.

DR. RAMIREZ: The placebo was receiving the low dose heparin?

DR. MACIAS: That analysis is for all patients, not split by those being treated or not being treated.

DR. RAMIREZ: Because I would not have spent too much money if I have it on anticoagulation and then I don't know if low dose heparin may be non-beneficial. I would just stop the low dose heparin while I give the drug and try to obtain this benefit without doing any further study.

DR. RELLER: Thank you, Dr. Ramirez.

Dr. Ebert.

DR. EBERT: I don't think that this is important for approval. However, it is something that we can randomize in a subsequent study. I think the results to date are compelling.

DR. RELLER: Dr. Wald.

DR. WALD: I agree.

DR. RELLER: Dr. Wittner.

DR. WITTNER: I believe it should be studied but it should not limit the approval of the drug.

DR. RELLER: Dr. Murray.

DR. MURRAY: Well, there is not even a hint of a benefit and, if anything, there might be a hint of an interference. So, I wouldn't let it hold up licensure. I am not sure it should be the sponsor's obligation to study

that effect. It might be, perhaps, an NIH-driven study. But I am not -- looking at the data here, it looks like it would take a huge trial based on these data, huge, huge.

DR. RELLER: Dr. Fleming.

DR. FLEMING: As we look at this table of the contrast between the on heparin and not on heparin, where the distinction is greatest is during infusion. I strongly concur with the sponsor's comments that such analyses have to be viewed with great caution. Not only is it the subset issue, these are improper subgroups and it is extraordinarily difficult to interpret results such as that. So, I look in particular at the at baseline contrasts and agree with what I have heard from my colleagues. I don't see this as data that would alter licensure or labeling.

Certainly, however, if this were to be approved, subsequent studies that would explore refining the optimal way to use heparin in conjunction could certainly be done.

DR. RELLER: Dr. O'Fallon.

DR. O'FALLON: I think that is the critical point. Not necessary for licensure. As to whether other studies are necessary, I am not at all convinced.

DR. RELLER: Dr. Munford.

DR. MUNFORD: I would like to see this studied further, just as I would like to see possible interaction between APC and glucocorticoids studied in more detail, but

I don't think that should influence the licensure.

DR. RELLER: Dr. Rotello.

DR. ROTELLO: I would also like to see this studied further but don't think it should affect licensure.

DR. RELLER: Dr. Warren.

DR. WARREN: I agree.

DR. RELLER: Dr. Suffredini.

DR. SUFFREDINI: I don't think it should limit the decision on licensure, but I would just bring, at least as I understood it, we have information based upon exposure to heparin, not total doses and a mixture of fractionated and unfractionated heparin were provided in the study. They were not designated. So, it is yet another confounding factor that needs to be looked at certainly in future studies.

So, I will leave it at that.

DR. RELLER: Thank you.

Dr. Lilly.

DR. LILLY: Because knowing whether there is an antagonistic interaction between these two drugs is so important, I believe that additional studies should be done, but that it should not hold up licensure of the drug.

DR. RELLER: Dr. Carcillo.

DR. CARCILLO: I would agree with the majority opinion.

DR. RELLER: Dr. Eichacker.

DR. EICHACKER: I agree.

DR. RELLER: Also.

Therapeutic heparin in sepsis-related DIC is controversial. I won't read through the entire paragraph. Were Drotrecogin Alfa (activated) approved, clinicians treating patients with severe sepsis and DIC will face a therapy choice of activated protein C or therapeutic heparin, but not both due to bleeding risks? Please discuss how such a choice might be made. Are there situations in which heparin use rather than activated protein C might be appropriate? Is there a need for further studies? If so, what type of studies would best address this question?

This is for discussion, comment.

Dr. Eichacker, your views. We will go around the table.

DR. EICHACKER: The issue about what the definition of DIC is here now becomes very important. DIC as it has been defined for the study is not something that someone would typically treat with therapeutic heparin. The use of therapeutic heparin in DIC is controversial when you meet the full criteria, I think.

So, at this point, I haven't seen any data to show -- I mean, there is no data that we have seen here looking at therapeutic heparin versus the effects of APC in true

DIC, where you have fragmented red blood cells, a falling fibrinogen and the other criteria that go into a true diagnosis of DIC. I have seen no data to say whether APC would be the preferable to therapeutic heparin. You would have to do a trial. Therapeutic heparin is the standard therapy and if one is referring to other kinds of conditions, such as thrombophlebitis, et cetera, where you were making a decision between activated protein C and therapeutic heparin, again, at this time, therapeutic heparin is the standard and you would really have to compare the drug to that in a study if you were to answer the question.

DR. RELLER: Dr. Carcillo.

DR. CARCILLO: I defer.

DR. RELLER: Dr. Lilly.

DR. LILLY: I would prefer a clinical trial to an observational study.

DR. RELLER: Dr. Suffredini.

DR. SUFFREDINI: I think the concern about increased bleed with therapeutic heparin and either concomitant therapy or doing a tradeoff is going to require that you address -- of course, more data is always important to have, but, you know, with the current presentation that we have and the materials that we had, the use of transfusions, fresh blood from plasma, platelets, PRBCs, I

mean, all those were increased in patients who were not on therapeutic heparin who received APC. It is a major concern in terms of bleeding risk and I think it has to be studied in a prospective fashion. We could do these tradeoffs.

DR. RELLER: Dr. Warren.

DR. WARREN: I essentially agree with that. I think, though, if the drug is licensed and a patient were to develop an absolute indication for therapeutic heparin, such as say a pulmonary embollist, then, in fact, one would need to stop the APC and use heparin because that is the treatment of choice.

DR. RELLER: Dr. Rotello.

DR. ROTELLO: I agree further studies need to be done. I feel that if you develop a condition that requires therapeutic heparin, the mortality of that condition weighed against the mortality of the acute sepsis needs to be considered before you can make a decision which drug to use.

DR. RELLER: Dr. Munford.

DR. MUNFORD: I agree. Nothing to add.

DR. RELLER: Dr. O'Fallon.

DR. O'FALLON: I have certainly heard many indications that suggest that this would be an extraordinarily complicated study to design, but perhaps one needs to be done.

DR. RELLER: Dr. Fleming.

DR. FLEMING: I defer.

DR. RELLER: Dr. Murray.

DR. MURRAY: I defer.

DR. RELLER: Dr. Wittner.

DR. WITTNER: I defer.

DR. RELLER: Wald.

DR. WALD: I defer.

DR. RELLER: Ebert.

DR. EBERT: I agree that a controlled study would be needed. Anything else would be speculative at this point.

DR. RELLER: Dr. Ramirez.

DR. RAMIREZ: How such a choice may be made and in a case of DIC, heparin will at least be controversial and we also have to wonder that activated protein C may be a better therapy for DIC than heparin itself because we are treating the cause of what is going to produce DIC. If I have a patient with sepsis and DIC and if I have the two choices, at this moment, I would consider a drug that probably is going to resolve the etiology.

Now, when we are looking at pulmonary embolism, it is a totally different story. Then these will be a definition that we have to consider what happened with the mortality of pulmonary embolism. For DIC, how the choice to be made, I will consider probably to stopping the heparin.

DR. RELLER: Dr. Christie.

DR. CHRISTIE-SAMUELS: Yes, I think an ICT should be done with regards to comparing heparin to APC in DIC truly defined.

DR. RELLER: Dr. Chesney.

DR. CHESNEY: I defer.

DR. RELLER: Cross.

DR. CROSS: I think patients who -- well, I think, you know, the interaction has to be studied, but the patients who have an absolute indication for heparin, the physician will have to just balance the relative risk of not being on heparin versus being on the APC for sepsis.

DR. SIEGEL: I just want to make sure I understand so I understand the advice. A couple of people have said where there is an absolute or clear cut indication for heparin, one will have to balance the relative roles. Nobody is assuming that clinical DIC per se is such an indication. You are talking about pulmonary embolists or whatever and that is sort of what we wanted -- right. Okay.

DR. RELLER: Dr. Archer.

DR. ARCHER: Nothing.

DR. RELLER: Dr. Leggett.

DR. LEGGETT: Nothing to add.

DR. RELLER: The next two questions have to do with safety and they are for discussion questions. The

overall assessment of the safety versus the benefit will come in the following question No. 10. So, for questions 8 and 9, a brief introduction.

Patients with severe sepsis were -- this is under Roman numeral V -- patients with severe sepsis, who were at increased risk for bleeding or excluded from the Phase 3 trial, including all of those in bullets listed. The number of patients experiencing serious adverse bleeding -- serious bleeding adverse effects during the Phase 3 study was 3.5 percent and those receiving Drotrecogin Alfa (activated) in 2 percent and those receiving placebo.

Then it goes on with further details. The essence we want to hear you comment on is given that the bleeding events are greatest during the infusion time, should further dose optimization studies be conducted; for example, fusion duration with the goal to minimize major bleeds while preserving efficacy?

Then, if licensed, should Drotrecogin Alfa be contraindicated in patients with conditions that led to exclusion from the Phase 3 trial because of high risk for bleeding? What if any other characteristics of patients at high risk for bleeding should be specifically identified in the product labeling?

So, what we could do here is go around, and Dr. Leggett starting, is say, one, do you need more studies for

dosing and then what sort of constraints if it were licensed, would you put into the labeling regarding exclusion of patients at higher risk for bleeding?

Dr. Leggett.

DR. LEGGETT: Regarding No. 8, I do not think further optimization studies are necessary for licensing, but I would hope that people would continue to look at this, just as we started off with huge doses of AZT, which we no longer use because we found they were too toxic.

In terms of No. 9, I think as I stated before that the contraindication should be the same as it was in the Phase 3 trial for the high risk of bleeding. I cannot think of any other characteristics off the top of my head for -- to labeling because the person with the thrombocytopenia as the example is given is possibly the one who has got the most DIC for which the drug is probably going to work the best.

DR. RELLER: Thank you.

DR. ARCHER: I agree with what was just said. It seems to me that dose optimization has been done, at least to the extent that it could be. I don't think you should hold up licensing. I think another study looking at more dosing and bleeding would be a very difficult study to do and it should be looked at.

I think that if licensed, it should have the

indications as we have said before that were done in the trials basically. Those patients excluded would have to be excluded in the label.

DR. RELLER: Dr. Cross.

DR. CROSS: I think the rationale for the dose presented seemed reasonable, but I also agree it would be very, very difficult to actually do the study suggested, but I think more information afterwards would certainly be useful. I think the exclusions ought to be those that were included in the study and I can't think at the time of any further characteristics of a high risk patient.

DR. RELLER: Dr. Chesney.

DR. CHESNEY: I concur with the previous speakers.

DR. RELLER: Dr. Christie.

DR. CHRISTIE-SAMUELS: No. I would address the issues of the labeling. I wouldn't do any definitive extra studies.

DR. RELLER: Dr. Ramirez.

DR. RAMIREZ: I agree. No extra studies. High rates for bleeding, somehow we need to identify -- the drug not to be used. These also bring the point in this drug is that we may use a drug, if we use it for the wrong indication, we may have a malpractice litigation because I am not aware of any of the antibiotics that we use for sepsis or any drug that usually we have a some side effect

that may kill a patient. This is going to be something that -- I am sure the physician is going to be willing to look into the exclusion criteria because you may be using something that may damage the patient.

DR. RELLER: Thank you.

Dr. Ebert.

DR. EBERT: I don't believe such studies will be necessary for approval. However, there is a pretty impressive inter-individual variation in the elimination of the drug. In the Phase 2 studies, the investigators did have the option of reducing the dose in patients who had an elevated APTT, whole blood APTT.

I am not sure whether the patients in the Phase 3 study, who experienced bleeding had an elevated APTT or not, but certainly there I think there is no question that that potentially might be something to look at as far as dose modification.

DR. RELLER: Dr. Wald.

DR. WALD: I don't believe any further study is required for optimization, but I do believe that all of the exclusion criteria with regard to coagulopathy should be observed here.

DR. MURRAY: I agree with Dr. Wald.

DR. RELLER: Dr. Murray.

DR. MURRAY: I agree except I guess my concern is

the exclusion for the platelets of less than 30,000, as was pointed out earlier, that might actually be of benefit. So, I would like to somehow get -- have some flexibility there perhaps. Perhaps contraindication is too strong for some of the exclusions, particularly that one.

DR. RELLER: Dr. Fleming.

DR. FLEMING: Clearly, it is an important issue to optimize benefit to risk with proper dose and schedule. With moderate sample sizes, we can probably look at how refinements in dose and schedule might alter safety. But, clearly, it will also potentially alter efficacy and then you are into very large scale trials. So, we are almost starting over again. We did have the data from the EVAA. It is a small Phase 2 study, but I found it interesting that at each of the dose levels, there was an indication of higher efficacy with the longer infusion period.

So, there is some -- there was some basis for them going to the schedule that they had chosen and I would anticipate that if we were able to reduce the bleeding, I would worry about in turn whether that might be reducing efficacy and it would be an extraordinarily hard thing then to address without doing another large trial.

The next question, No. 9, certainly, yes, I would say if licensed, the agent should be contraindicated in those conditions that were related to high risk for

bleeding.

DR. RELLER: Dr. O'Fallon.

DR. O'FALLON: I agree.

DR. RELLER: Dr. Munford.

DR. MUNFORD: I agree.

DR. RELLER: Rotello.

DR. ROTELLO: I agree.

DR. RELLER: Dr. Warren.

DR. WARREN: I agree with Question 8. For Question 9, I would only raise a point that a lot of people are now being treated with steroids, both for ARDS and also there was actually a French trial suggesting it may be helpful, low dose steroids. Since a lot of the bleeding was due to GI bleeding, I think if it is licensed, it should be commented on and if it is not licensed, I think that should definitely be part of another trial because I think that (a) we don't know about synergistic either toxicity or synergistic benefit and I bet that physicians will try to use both.

DR. RELLER: Dr. Suffredini.

DR. SUFFREDINI: With regards to No. 8, it shouldn't hold up licensing, but I mean the issue of distinguishing between the anti-inflammatory effect and the anti-coagulant effect and dose optimization is something that, you know, needs to be looked at obviously. But I

don't believe that it would require a substantial effort to address that issue.

I do agree that No. 9, that the exclusion criteria that we used in the Phase 3 trial for high risk patients should be kept in there. I guess my only concern about the issue about the platelets is that we haven't been provided data specifically in severe DIC with low platelet counts to tell us whether that was beneficial or harmful. We don't have any data on it.

So, I just don't know what to address with regards to that caveat that we have to be concerned about people with severe DIC. We have no data. So, I can't make an exception to what was already defined here as the exclusion criteria.

DR. RELLER: Thank you.

Dr. Lilly.

DR. LILLY: I do not believe additional dose optimization studies are necessary and I do believe that the document should be clear as to the exclusion criteria used in the trial.

DR. RELLER: Dr. Carcillo.

DR. CARCILLO: I would like to take a moment to just show the differences between babies and adults. A baby has about this much blood in their body, a newborn 3 kilo, and then by the time your child is a year of age, they have

approximately three of these. Then you as an adult have approximately four of these. So, it is extremely important to address this question on an age-dependent basis.

A given amount of bleeding from a newborn can be catastrophic, but for me it would be considered a relatively easy event. From the standpoint of what I am seeing -- and, again, the data I know is not in its final form, but from Dr. Lindblad's production, we have bleeding instances that rival what we see with pediatric ECMO(?).

Now, let me say what those are. From what I see, there is a 21 percent instance of bleeding associated with the drug. There is a 5 percent of 4.8 percent incidence of serious bleeding. As Dr. Gerard pointed out, one of those was associated with meningococcemia, but even if you take out the meningococcemic and the meningococcemic patients, as predicted by the biological plausibility, you have a high bleeding risk.

Most bleeding risks are also compounded by age-dependent differences. As you know in children, we don't use heparin or subcutaneous heparin. They don't tend to have thrombosis. They tend more towards bleeding. So, I think, very importantly, this has to be looked at.

In terms of contraindication in patients because of high risk of bleeding, I think this needs to be looked at carefully as well.

DR. RELLER: Dr. Eichacker.

DR. EICHACKER: Yes, I don't think it necessarily deserves study but it is concerning that now that the drug in uncontrolled use is associated with an incidence of intracranial hemorrhage, which is almost ten times its rate during the study. It certainly has to be monitored if the drug was to be used because I don't know whether that is going to escalate as other people use it. It is a concern.

Yes, all the exclusion criteria should be included.

DR. RELLER: I agree, no further dosing studies with the appropriate exclusions in the labeling if it were approved, as has been mentioned earlier.

We are now at Question 10. Overall risk/benefit assessment. Do the available safety and efficacy data support an indication for the use of Drotrecogin Alfa (activated) in adult patients with severe sepsis with any of the limitations discussed above?

Dr. Eichacker?

DR. EICHACKER: My concerns about how the study unfolded, the change in inclusion criteria, the change in drug make this -- make it very difficult for me to say that this drug should be approved. I don't think it should be approved at this time. I think it has to be studied additionally.

DR. RELLER: Thank you.

Dr. Carcillo.

DR. CARCILLO: Well, I am a pediatrician. My viewpoint is from the study is yes.

DR. RELLER: Dr. Lilly.

DR. LILLY: I believe that there is convincing evidence that this drug saves lives and it should be improved.

DR. RELLER: Dr. Suffredini.

DR. SUFFREDINI: I think the combination of two studies confounds their interpretation of the data and I think a confirmatory trial should be performed.

DR. RELLER: So, that data as of the moment are not sufficient.

DR. SUFFREDINI: Not sufficient, right.

DR. RELLER: Dr. Warren.

DR. WARREN: I would say no. I think there should be a confirmatory trial. I am persuaded in part by the fact that I am concerned about the lack of a release test. In fact, if there was another trial, I would be concerned that the lot be very, very carefully studied in animal models because otherwise you could have a situation where we wouldn't even know how to interpret the next trial. So, if there was another trial, I would urge that there be animal testing of that lot.

DR. RELLER: Dr. Rotello.

DR. ROTELLO: I think, no at this point, pending delineation of some of the questions the panel has brought up in previous discussion.

DR. RELLER: Dr. Munford.

DR. MUNFORD: I agree.

DR. RELLER: Dr. O'Fallon.

DR. O'FALLON: My overall gestalt -- and statisticians, I suppose, aren't supposed to have gestalt. We are supposed to have data -- was positive in the sense that I thought there was persuasive evidence, but it says overall benefit/risk assessment and the concern I have is that the benefit/risk assessment was very, you know, kind of basic. We saw whether a person lived or died as being the only criteria and Dr. Fleming had us looking at a beautiful graphic with multiple colors in it that persuaded me to some extent that maybe we needed to see a little bit more of quality of life type of assessment.

My quality of life in the intensive care unit might not be a great deal better than in the coffin. I am not quite sure how I feel about that since I am hopefully not near either of those places personally. I think also that my gestalt is seriously confounded by the fact that the study does seem to really be two different studies as most of my previous colleagues have said.

It is a shame at this stage you all tell me that sepsis has been studied for 30 years, that we had to design a study that then had to be redesigned practically within the first year. So, I am really flipping a mental coin here at the moment, I guess. I am going to stay with my gestalt and say yes.

DR. RELLER: Dr. Fleming.

DR. FLEMING: Well, I hope the reasoning and justification for my answer here is going to be more useful to the FDA than my actual vote because my vote is yes and no.

[Laughter.]

Let me give my reasoning. I am most impressed by the fact that this was a very large study. We have addressed a number of concerns that have been clearly articulated about imperfections. At the same time, this was a major accomplishment and many aspects of the study were extremely well done. It yielded a significant result on survival. In the context of a myriad of such studies done in the past, it certainly has to be one of the most impressive from a favorable perspective.

What cautions me a bit about that, though, are some of the issues that have already been alluded to. One is the 6 percent difference in survival is in essence for the most part people are in the hospital. I don't know

specifically what the implications of that would be, how much does that compromise the level of survival benefit?

Other endpoints we haven't discussed very much, organ function, effects on that, health economic impact effects. They are pretty modest. I might have hoped to have seen a bigger effect when I looked at those myriad of measures. So, those were -- those also somewhat tempered my sense of strength of efficacy.

Clearly, there is some risk that we have discussed greatly, the most important being the bleeds and I am more concerned from what I have heard today about the intracranial hemorrhage as well. I don't understand much about that because it was just presented to us today, but it does lead to some caution.

I think if I believed that these data are the truth, I probably would be persuaded more toward the yes side, but these are estimates. These are maybe very informative estimates, but these are estimates nevertheless. There are three factors that caution me about how reliable these estimates are.

One of them is the great discussion that we have had about consistencies and inconsistencies across subgroups. For the most part, much of the subgroup analysis discussion is more heat than light, but I do think there is signal there relative to the low risk patients.

We have also had a lot of discussion about the uncertainties as to whether in essence these are two trials based on time. If, in fact, we do break into the first group versus the second group, as was given in the briefing document, we have got a very nice positive study and we have got a negative study. Study results tend to be less persuasive when there are inconsistencies, any study if you subdivide enough and subgroups will show inconsistencies, but I think there are some real inconsistencies here.

A second point, this study was stopped early using very -- very appropriately using methods, nevertheless, when you do stop a study early, there is statistically some overestimate of the magnitude of treatment effect. So, from that perspective, it is probably modestly -- although that is maybe about a 10 percent. So, if we are estimating a 6, probably an unbiased estimate would be about a 5 to 5 1/2 percent improvement.

The final point, though, that concerns me, and I am a frequentist rather than an abasian(?), so in a certain sense I hate to bring this up, but I can't help but look and interpret these results in the context of historical evidence. We heard the sponsor earlier today talking about the interpretation of the data from previous trials, when validation studies were consistently negative.

Now, I think the essence appropriately of their

point was that was, though, based on having seen data exploratory subgroups that couldn't be confirmed. Nevertheless, there is reason to argue that confirmatory trials are extremely trials are extremely valuable. We haven't discussed this today. What is your standard, FDA? Do you want two adequate and well-controlled trials or is one study enough?

This study at best meets the standards for strength of evidence of one positive trial. In the context of a myriad of previous agents that were found to be in essence negative, if you begin with the sense that the vast or a large majority of these agents, because of the incredible challenge of having a survival effect in this setting are likely to be negative. Then there is a fair -- it is called predictive probability -- there is a fairly high probability achieving a statistically significant positive result is actually a false positive.

When you do a confirmatory study, it will be negative. So, with these issues interpreting these data, I go back to what I said about three minutes ago. If these data I knew represented the truth, I would be persuaded towards supporting a recommendation of an approval, but an approval in a restricted manner as we have discussed earlier, which is at least from my perspective not including the ped population and the low risk that I believe those

should be studied separately in another trial.

On the other hand, taking into account all of these other considerations of particular caution, I could be persuaded that the right answer is to do another trial in its entirety.

DR. RELLER: Dr. Murray.

DR. MURRAY: I think I am going to refine the being on the fence and go 60 percent yes, 40 percent no. But coming from the usually seen antibiotics, where there are confirmatory trials, that is probably, again, my hold up as well, that we haven't -- there isn't a confirmatory trial here. But I am still going to come down as a yes.

DR. SIEGEL: By the way, since you asked about the legal standard, I am sure many of you are aware we have a document about evidence of effectiveness for the Agency and there is not an absolute requirement that there be two trials showing efficacy. There is requirement for a trial and confirmatory evidence that can come from various sources. We discussed at some length settings in which one trial may be -- may suffice and that includes a compelling trial on a mortality endpoint that is often felt that it is unethical or impractical to try to do a second trial, once you have a compelling trial and a mortality endpoint.

I recognize that, you know, a lot of what this discussion goes around, a lot of what Dr. Fleming's comments

addressed, is how compelling is this trial. So, a lot of the comments are suggesting that other trials are potentially feasible. But suffice it to say, there is not a black and white applicable standard here that says -- in our evidence of effectiveness that says there needs to be -- absolutely needs to be two trials or there only needs to be one.

DR. RELLER: Dr. Wittner.

DR. WITTNER: I am going to come down on no. I think the reasons for coming down on no is because I am concerned that there was a change in the drug in the middle of the trial and the change in the patient criteria. I am also somewhat concerned based on the functional status data that Dr. Forsythe showed, which gave some sense that perhaps that 6 percent differential is really not 6 percent.

DR. RELLER: Dr. Wald.

DR. WALD: I think this is very tough. I just feel that this drug was performing well and it sort of performed better and better as time went along and I am not sure exactly what that reflects, but I do think it is the truth. I think that if we don't approve it, we will be denying people who would benefit from it.

So, at least for my self consistency, I would vote to approve.

DR. RELLER: Dr. Ebert.

DR. EBERT: I think in an ideal world if we were able to approve this drug with the -- to the patients who were enrolled in this study with the restrictions that we have talked about, as far as restricting it to patients who would be at higher risk of mortality, I think this would be a no-brainer.

Unfortunately, my concern is that the ultimate use of this drug might include, first of all, the low risk population and also probably more importantly the patients who were excluded from the study and, therefore, I would vote no.

DR. RELLER: Dr. Ramirez.

DR. RAMIREZ: I think I was convinced in the discussion today that in the second part of the protocol, this drug was used in patients with severe sepsis without serious comorbid conditions, that the patients were previously healthy that then developed severe sepsis. This is usually one that you can clearly define severe sepsis with a source of infection.

These patients were sick because we see the advantage with severe APACHE scores. Then in my mind I see -- I don't see the multi-organ failure in the unit. In my mind I see the person arriving from the community, young person with trauma, sepsis or the pneumonia, sepsis and this group of patients that are in my mind, I have no question

that for every five of these patients that are going to die, one is going to be saved by the drug.

The question here says with any of the limitations discussed above. If I can figure out to use the drug in the patients that were studied, my answer is yes.

DR. RELLER: Dr. Christie.

DR. CHRISTIE-SAMUELS: My answer is yes with postmarketing surveillance to look at bleeding issues and also to look at quality of life issues.

DR. RELLER: Dr. Chesney.

DR. CHESNEY: Like Dr. O'Fallon, my gestalt is yes and I feel like we need to move ahead with any potential treatment for sepsis, which everybody has articulated well, but we haven't done very much.

I have a bad feeling that this going to turn out just as all the other ones have, as Dr. Opal indicated, but I also appreciate what Dr. Ramirez said about the fact that if this drug is not limited in its use and if people ignore that, there could be very serious consequences for the patient and medical-legal issues. So that I would restrict it to patients with more serious disease; namely, the APACHE groups, 3 and 4 for sure and maybe 2, and I would exclude its use in the group that was excluded in the trial.

DR. RELLER: Dr. Cross.

DR. CROSS: I am concerned that there were two

marked differences in the outcomes of the study done both before and after the amendment and we don't have any adequate explanation whether it is the difference in the drug, which is extremely hard to make or the patient population. In the absence of having an explanation for that, I do think we need a confirmatory trial. Before doing so, I would just like to echo the point that Dr. Warren made that we need to have some added -- the efficacy of this agent, perhaps, in an animal model before proceeding further with a large scale study.

DR. RELLER: Thank you.

Dr. Archer.

DR. ARCHER: I haven't heard anybody talk about costs and I haven't seen a cost benefit analysis. I realize you can't put a value on a human life and I am sure that is one of the considerations, but this is a real budget buster potentially and particularly for small hospitals, where it may not be as limited as it is in a big hospital, like some of the ones we work in. I mean, it may just be used fairly indiscriminately, I am afraid, if it -- so I would like to see some of the issues that were raised here and that are unknown so that we can clearly define how this drug should be used so that it can be used in the right circumstances and that can be enforced.

DR. RELLER: That is a yes or a no?

DR. ARCHER: That is a no.

DR. RELLER: Dr. Leggett.

DR. LEGGETT: It seems like we are going to go down this approvable path meeting after meeting with the 60 percent yes, 40 percent no, et cetera. I think that there is -- and the reason I think everybody is hesitant is that there is some pathophysiologic plausibility here. Then we are worried about the benefit versus risk, not only the bleed versus saving somebody's life, but, you know, the benefit of a hospital stay in a vegetative state versus dying or, you know, to characterize.

I think that one thing that I would like to have us consider as well is the different backgrounds of the people who made the statements. I was sort of surprised that generally in my hospital and I am sure elsewhere the infectious disease doctors tend to be the sticklers and the cowboys or the cardiologists and, you know, the critical care folks in some sense.

But in this case, probably the majority of the cowboys came down saying no and the majority of the sticklers said yes, maybe. So, I am sort of -- I don't know how to interpret that. But to point out another thing that we haven't talked about and that this is an interaction between a variety of fields that always interact a little bit hesitantly at times because we all have different legs

of the elephant.

Whether there should be ongoing clinical monitoring, I think, is for sure. How that is best done, we can leave it up to the FDA and I think that a confirmatory trial should be done. If that cannot be done or judged not to be, then I would say yes, that it be approved.

I am in sort of the approval camp, sort of like, you know, in the sense that if it is feasible for all the reasons that we talked about in terms of the money before or doing a group of -- where you divide them down them down the median of the three different severity things that we talked about, 3 and 4 versus 1 and 2 of APACHE, three or more organ failure versus -- you know, and you can get to a small, not huge trial again. If that is feasible, then I would say that -- through the confirmatory trial before, if that is not feasible, then I would say go ahead and license.

DR. SIEGEL: Let me try to get some clarification on this point. If we don't approve it, I assume it would be feasible to study the same population or even a broader population, not excluding chronic disease. Are you suggesting -- but you would like to see us not approving it but studying only a subpopulation?

DR. LEGGETT: No, I would say approve it but if there is some way that we can get at further tests to in terms of the confirmatory trials, I would urge that be done

for all the reasons that Dr. Fleming and Dr. O'Fallon pointed out.

DR. RELLER: There is one more vote and it is a no.

The WHO defined health as more than the absence of illness. As I heard these discussions today, there is more to life than absence of death. I suspect that there may be a winner here, but I would like to know it and not go down the same path that has been gone down before. There are basically two studies. There are many hesitations that have been voiced in the committee.

This is an opportunity to do it right and if those diverging, increasing of effectiveness that we saw in the latter half of the trial held up and stayed constant, then we would have a confirmatory trial and we would have the first effective agent for the kinds of patients described. I think that would be an incredibly valuable contribution. I do not believe that we are going to get there with that definitive answer if this is approved as is now.

The next item, pediatric studies. We are item No. VII. We are to the last several questions. I will not take the time at this hour to read all of the issues having to do with pediatrics. They were discussed at some length in the interchange that took place before we came to the questions.

So, we will now go to No. 11. This is for a vote.

Is severe sepsis in children sufficiently similar to severe sepsis in adults, such that it would support extrapolation of the efficacy of Drotrecogin Alfa (activated) from adults to children, based on PK and PD data in lieu of adequate and well-controlled efficacy data in pediatric patients?

Dr. Leggett.

DR. LEGGETT: This is the sort of similar sort of vein as to what was said before. I think, yes, they may be pathophysiologically similar, but, no, in terms of the risk/benefit for all that sort of low risk population we have been talking about. I don't think they are similar and I think, therefore, that a trial needs to be done and if it is true that there are 45,000 cases per year in the pediatric group, I thin we ought to be able to come up with more than 300 in a trial.

DR. RELLER: Actually, for the sake of time, do you have -- on 12 and 13, do you have any additional comments to make on those components, Dr. Leggett?

DR. LEGGETT: D-dimer is not helpful, at least not in our hospital. Everybody is positive. So, I don't see that as being useful at all.

Then No. 11, I am sure the pediatrician can tell us more about the trial data, but I think I just already pointed to that.

DR. RELLER: Okay. So, as a format for the

subsequent members for concluding our deliberations, yes or no with any comments on No. 11 and any comments on the subcomponents 12 and 13.

Dr. Archer.

DR. ARCHER: I defer to the pediatricians. I have heard conflicting data and I can't really decide on whether trials should be done. So, I respectfully defer.

DR. RELLER: Dr. Cross.

DR. CROSS: I would also defer to the pediatricians on that, but I would also like to point out that fairly large studies have been done on the pediatric population in sepsis, certainly, looking in terms of IV gammaglobulin. I assume that a similar type of patient population would be available for this study.

DR. RELLER: Dr. Chesney.

DR. CHESNEY: I would like it to go in the record that two internists deferred to a pediatrician.

[Laughter.]

I would like that framed and I would like a copy. They are forever my close friends.

I think this absolutely has to be studied in children and I wouldn't even pretend to know how to study it and I would leave the answers to 12 and 13 to my intensive care colleagues.

DR. RELLER: Dr. Christie.

DR. CHRISTIE-SAMUELS: I agree with the FDA summary, pediatric summary as presented, that these -- with regards to PK and PD effects and also the bleeding events. What is different with regards to organ failure, it is just one organ failure and the mortality. I think with regards to Question 12, I am not so sure that this is applicable.

Question 13, I think Dr. Carcillo is going to give us something very interesting with regards to how this should be done. He alluded earlier on to the fact that we have a lot of patients, pediatric patients, who can be studied with sepsis and I would love to hear what he has to say on that.

DR. RELLER: Dr. Ramirez.

DR. RAMIREZ: I defer to the pediatricians.

DR. RELLER: Dr. Ebert.

DR. EBERT: Based on the safety data, I am not comfortable with extrapolating the results in adults to those in children. I think what we need is some type of a controlled trial to try to assess the true delta between treatment and no treatment and only then can we really assess the risk/benefit.

DR. RELLER: Dr. Wald.

DR. WALD: I agree that separate studies need to be done in the pediatric age group. Although the pathophysiology of sepsis is similar, I think the etiologies

are different. There is a lot more bacteremic disease. There is a lot more viral sepsis. I think those deserve separate inquiry and I also think the risks of this drug in the children have not been well-delineated.

DR. RELLER: Dr. Wittner.

DR. WITTNER: I agree with Dr. Wald.

DR. MURRAY: I would just like to say that if the pediatricians deferred every time we were voting on adult disease, we wouldn't have very many votes. So, I will -- I do not think the drug should be approved in pediatrics right now. I think it will be out there for individual cases off label. I would like to see it studied.

DR. RELLER: Dr. Fleming.

DR. FLEMING: I would like to make a distinction between a partial and a total extrapolation. In essence, as I see it here, we are being asked to make a complete extrapolation. There is no controlled data and we are asking are these children sufficiently like the adults that we can completely extrapolate. I believe the answer to that is no.

However, I do concur that a partial extrapolation is going to be necessary and my sense is another trial should be done of some type and in that trial, I would hope the children would be an important representation. Three to 500 children in a study that has many more patients than